



The Role of Environmental Factors in Medically Unexplained Symptoms and Related Syndromes: Conference Summary and Recommendations

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This monograph of peer-reviewed articles is based on presentations at the conference “Environmental Factors in Medically Unexplained Physical Symptoms and Related Syndromes” held 10–12 January 2001 in Piscataway, New Jersey, USA. The purpose of the conference was to determine research priorities for elucidating the role of environmental factors in medically unexplained symptoms and symptom syndromes. These include conditions such as chronic fatigue syndrome, multiple chemical sensitivities, sick building syndrome, Gulf War illness, and the like. Approximately 1 1/2 days were devoted to plenary talks and 1 day was devoted to break-out sessions to discuss epidemiologic, psychosocial, and experimental research. Recommendations were made for a series of epidemiologic, psychosocial, and experimental research approaches, with acknowledgment that nosology issues are clearly fundamental to advancing understanding of these conditions. *Key words:* environment, indoor air, psychology, research, symptoms. *Environ Health Perspect* 110(suppl 4):591–595 (2002). <http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/591-595kipen/abstract.html>

Recommendations

This *Environmental Health Perspectives* monograph is a compilation of peer-reviewed articles based on presentations at the conference “Environmental Factors in Medically Unexplained Physical Symptoms and Related Syndromes” held 10–12 January 2001 in Piscataway, New Jersey, USA. The conference focused on the development of a research agenda to help investigators understand the role of environmental factors in a diverse, yet strikingly similar group of illnesses and syndromes. These may present either endemically, such as chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS), fibromyalgia, post-Lyme disease, electromagnetic sensitivity, and somatization; or epidemically, including outbreaks of sick building syndrome (building-related illness), systemic complaints associated with breast implants, and Gulf War illness. All these entities are remarkably similar in symptomatic presentation and in the limited approaches employed by scientists to investigate them. The similarity of the complaints across these syndromes has not been widely acknowledged nor has this commonality been exploited by the scientific community to advance our public health and therapeutic approaches to such vexing, persistent or recurrent, often disabling, and apparently related issues. Currently, most of the demands for response are based on putative etiologies for the symptoms of the various conditions and often lead to specification of a public health agency for response (environmental health agencies for MCS and Gulf War illness, infectious disease agencies for CFS, and mental health for somatization). Yet, the symptoms posited to result from

these dissimilar causal agents show remarkable similarity; and to the extent they have been studied, the victims of one disorder frequently qualify, on the basis of symptoms, for other disorders as well. Thus, consideration of these symptoms and syndromes in concert is long overdue, and this was the overriding rationale for this conference.

Objectives and Organization of the Conference

The primary objective of this meeting was to convene a diverse group of expert researchers from the United States, Canada, and Europe to address the relationships between medically unexplained physical symptoms and environmental exposures.

The experts were asked to consider the following questions in formal presentations and group discussions:

- What are the nature and mechanism of the relationship(s), if any, between environmental exposures (both acute and chronic) and symptoms without apparent disease?
- How do we determine an optimum nosology to classify these symptom complexes as they

arise, particularly, how do we best distinguish for individuals and groups between medically unexplained physical symptoms related to an environmental exposure and those relatively unrelated to exposure.

- What experiments or epidemiologic studies would best clarify or refute examples of the above distinction between conditions related to the environment and those that exist relatively independent of environmental influences?

Each invited expert made a presentation and submitted a manuscript reflecting her/his own research interests. During the course of the 2 1/2-day meeting, discussion groups were held in which the focus was on responding to the three questions above, although explicit answers were not generated for all questions, and all answers to date are incomplete. Presentations were made and then manuscripts were submitted, which summarized or expanded upon the oral remarks.

Epidemiology of Unexplained Physical Symptoms Attributed to the Environment

The first group, encompassing seven papers, addresses the epidemiology and phenomenology of unexplained symptom disorders widely attributed to, and named after, environmental factors.

In our overview of the problem, we cited evidence supporting both an overlap in the disorders and the important role for environmental factors in many of these constructs of illness. The logic of intertwining psychosocial with environmental investigation was emphasized.

Richard Kreutzer (1), a medical/environmental epidemiologist outlined the epidemiologic challenge of linking chemical exposures to symptoms from a health

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We are greatly indebted to all who gave so much of their creativity to allow these recommendations to be made, and for the support of several U.S. government health agencies including the National Institute of Environmental Health Sciences (NIEHS), U.S. Environmental Protection Agency, Centers for Disease Control and Prevention (CDC) (grant U50CCU214463), and National Institute of Mental Health, as well as private industry support from the American Petroleum Institute and ExxonMobil Biomedical Sciences. In addition, N. Fiedler and H. Kipen were partly supported by CDC, National Institute for Occupational Health and Safety (grant R01 OH03691), and NIEHS Center grant (Cooperative Agreement ES05022). This breadth of support for this conference augurs for increased recognition of the common challenges presented as we attempt to understand what lies beneath the enigma of Medically Unexplained Symptoms and their relationship to the Environment (MUSE).

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department point of view. He emphasized problems with labeling, the need for case definitions, and consideration of alternative models for causation.

Anne Spurgeon (2), a psychologist, proposed a biopsychosocial model of illness in an attempt to leap over the “mind–body” dualism that bogs down so many debates on this issue with the often unanswerable question, “Is it real?” She gave an enlightening example of some of her own perceptual and neuropsychological investigative work into an outbreak of symptoms among farmers chronically exposed to pesticides. This outbreak is known as “The UK sheep-dip story.”

Leonard Sigal (3), a rheumatologist, and psychologist Afton Hassett, discussed Lyme disease as an example of a condition sometimes characterized by medically unexplained symptoms erroneously attributed to an infectious agent.

Simon Wessely (4) discussed his own prolific research and the current state of knowledge on the nature and causes of the symptomatic epidemic known as Gulf War syndrome 10 years after it first appeared. This syndrome remains one of the quintessential examples of a high profile outbreak in which widespread assumptions of environmental causation have not led to compelling data to support environmental causation.

Raymond Neutra (5,6), a distinguished environmental epidemiologist, together with his colleague Patrick Levallois, provided two pieces on the phenomenon of electromagnetic hypersensitivity. The first, a general review of the published literature, concludes that there is a very limited scientific database that could be used for risk assessment. The second was a survey, modeled after Kreutzer and Neutra’s groundbreaking epidemiologic work on chemical sensitivities, exploring the population prevalence of symptomatic complaints related to perceived EMF exposure, and also noting its relationship to correlates of sensitivity to chemicals (7).

Finally, Evelyn Bromet (8), a psychologist distinguished for her study of environmental/occupational problems, described a detailed study of the health concerns of women evacuated following the Chernobyl power-plant explosion, concluding that long-term health complaints did arise from the disaster and that they exert their greatest impact in vulnerable and disadvantaged groups.

Psychosocial Mechanisms and Classification of Unexplained Physical Symptoms

The next section of articles was written by mental health researchers, whose emphasis has been on the psychosocial mechanisms and classification of medically unexplained

physical symptoms other than environmental health problems.

Javier Escobar (9), on the basis of his extensive psychiatric research into somatization, provided an assessment of the frequency, classification, research, and treatment for such symptoms in clinical settings, which provided a valuable perspective on how environmental health investigators need to interact with and understand prevailing healthcare paradigms to effectively advance our response to these problems.

Carol North (10), a distinguished psychiatric epidemiologist studying the effects of trauma, reviewed the pitfalls of doing post-trauma research and the need to carefully evaluate symptom reports according to many key methodologic criteria.

Charles Engel (11) an Army psychiatric researcher, discussed the challenges that medically unexplained physical symptoms present to practitioners, especially in the setting of “contested” exposures and causation. He offered a number of therapeutic strategies for improving outcomes based on a collaborative care concept.

Biological Mechanisms for Unexplained Symptoms

The next section of articles begins to address the third question on experimental models that may yield insight into the nature of medically unexplained symptoms and contributions of environment to their genesis. Not surprisingly, many of the models focus on the nose and upper respiratory tract.

Dennis Shusterman (12), an occupational physician and upper airway researcher, reviewed the panoply of upper airway syndromes associated with either irritant, allergic, or odorant mechanisms. He provided an excellent outline, based on pathogenic mechanisms, from which to deconstruct a variety of symptomatic complaints. These mechanisms also guide the experimentalist in terms of parameters needing control in controlled exposure challenge experiments.

Glenn Greene (13), in conjunction with Howard Kipen, proposed a hypothesis explaining chemical sensitivity based on interindividual differential function of the controversial vomeronasal organ, situated in the anterior nose.

Michael Hodgson (14), an occupational physician and indoor air quality expert, reviewed the myriad exposures and stressors associated with symptoms and commonly known as sick building syndrome. He identified many likely mechanisms that may explain unexplained symptoms in a number of settings and attempts to integrate this with psychological aspects of symptomatology.

Susan Tarlo (15), a pulmonologist, presented an elegant investigation demonstrating

a high rate of susceptibility to panic attack induction among patients with MCS (referred to in the paper as idiopathic environmental intolerances). This has both important therapeutic implications and interesting mechanistic implications for the relationship of MUS to panic, which is well known to have both physiologic and psychologic correlates.

Benjamin Natelson and Gudrun Lange (16) summarized the work of their group and others in a search for underlying physiologic abnormalities among CFS patients. They discussed their promising investigations recently using functional magnetic resonance imaging that seek to document that CFS patients have an underlying mild encephalopathy. They described cogently the potential for overlap of psychiatric diagnostic nomenclature with demonstrable, although rarely clinical, physiologic dysfunction.

Research Recommendations from the Conference

The recommendations presented below are the work of all attendees at the conference and are summarized by the authors. The responses and recommendations, some focusing on additional implicit issues as well as on the questions listed above, are summarized under categories responsive to the spirit of the above questions: Policy and Procedural Recommendations; Nosologic Considerations; Recommendations for Epidemiologic Research; Recommendations for Experimental and Mechanistic Research.

Policy and Procedural Recommendations from the Conference

The necessity of interdisciplinary approaches is recognized, and workshops facilitating such research are key to advancing this aim. A government agency or interagency working group is needed to be responsible for this group of problems. A scientific society should be identified as a focal point through which relevant data could be regularly presented and debated. This is not a small challenge because of the apparent gap in interests and directions of organizations such as the Psychosomatic Society, the American Thoracic Society, the Society for Indoor Air Research, the Neuroscience Society, and the International Society for Environmental Epidemiology, just to name a few of those at which a number of relevant papers are presented. Some regular forum for presentation of relevant research, such as the present ad hoc conference, needs to be developed and made attractive to the diverse group of researchers.

One suggestion was that in order to engage greater governmental interest, a formal thought exercise might be conducted, in which, after possible explanations for

symptoms are identified, the consequent policy options for prevention, treatment, and rehabilitation could be examined. Data gaps, including those that are fundamental, such as prevalence of various manifestations of unexplained symptoms and their syndromes, would need to be identified. Such an approach might empower a greater and more unified governmental stake in these problems.

Nosologic Recommendations from the Conference

In terms of research, attendees emphasized the desirability of flexible case definitions. This means that the literature has demonstrated enough overlap between putatively separate entities, that it is desirable to think of any one definition in terms of various others. Further definition of the degree and nature of such overlap can result from cross-sectional (and cross-disciplinary) studies that incorporate more than one of the available definitions, and researchers should strive to incorporate standard definitions along with any novel ones. Funding agencies should acknowledge the greater burden of working with multiple candidate definitions.

The conditions being considered need to be rigorously evaluated for the extent to which they meet established criteria to be considered as distinct nosologic entities: The Washington University criteria were specifically recommended for evaluation: *a*) core characteristics, *b*) laboratory studies, *c*) family studies, and *d*) follow up studies (17). It was recommended that CFS and fibromyalgia might be the best places to begin such a formal exercise, because of the relatively greater volume of peer-reviewed research investigations available that directly address them.

We recognized that various published scales for somatization have low levels of agreement, suggesting that if somatization is a disorder, we have yet to isolate its most salient characteristics. We also recognized that perhaps high levels of symptoms, somatic aspects of depression and anxiety, and hypochondriasis are not fully distinct. We felt that even in the context of recognized psychiatric entities such as obsessive-compulsive disorder, schizophrenia, and depression, debate continues about which ones qualify as disease entities, and thus continued nosologic research, incorporating unexplained symptom syndromes, is a priority.

Current cross-sectional data on prevalence suggest substantial degrees of subthreshold (nonclinical) symptoms, which may become problematic in certain individuals or certain situations (7). The relative contributions to this subthreshold symptom prevalence of biological, psychological, or social factors are unknown. It is also not known whether such relative contributions

differ in individuals who have more severe manifestations that lead to clinical presentation for medical care. Such etiologic/mechanistic considerations will have substantial impact on nosology and addresses a fundamental question common in medicine and mental health as to whether certain disorders exist on a continuum or are truly discrete. Novel and multifaceted research approaches are indicated to disentangle the relative, and perhaps simultaneous, contributions.

When adequate peer-reviewed research supports a case-definition change, it must be done carefully so that comparison with historical studies is not hampered.

Epidemiologic Recommendations

Integrating with large scale prospective cohort studies such as has been done with the U.S. National Collaborative Perinatal Project (18) was considered an optimal strategy. Creation of new cohorts for longitudinal evaluation of progression and natural history was recommended. For example, those individuals who have been identified in cross-sectional population studies as having subclinical symptoms in the absence of a clinical presentation of illness, could be followed prospectively. We recognized as a limitation to this line of investigation that some large psychiatric epidemiologic studies now under way have chosen not to include standard definitions of somatization, let alone the less well-established conditions we discussed.

The prospective study of populations at risk for exposure to chemical or other significant stressors was deemed a high priority. Suggested examples, some of which have already been studied cross-sectionally, include children living near industrial facilities plagued with significant chemical releases; military recruits; police and fire department recruits; children living in violent inner cities; and children living in hurricane-prone areas. Some of the various populations enumerated by the Agency for Toxic Substances and Disease Registry in Atlanta, Georgia, USA, as living in proximity to hazardous waste sites may also be ripe for exploration of the relationship of symptoms to the sites, and these may lend themselves in particular to longitudinal study. Use of quasi-experimental interventions with variable messages about risk being transmitted to two similarly exposed populations was one specific recommendation.

Development of rapid research response capabilities, such as linking the Washington University Disaster Study Group to a capability such as that represented by the California Department of Health's chemical sensitivity questionnaire, would be another example of promoting cross-disciplinary investigations.

Another example is The British Chemical Incident Registry. The registry may provide an opportunity for researchers to study chemical release incidents that do not result in widespread acclaim as well as those that do. This would enable investigators to examine—relatively independent of media influence—the factors leading to greater individual and population distress.

Experimental/Mechanistic Recommendations

We agreed that the opportunity for experimental science to contribute to our understanding of the relationship between medically unexplained symptoms and the environment was enormous (almost by definition if environmental agents do make a non-perceptual contribution), although largely unrealized to date. Despite the numerous unsuccessful attempts of investigators to document a clinically or epidemiologically useful marker (toxicologic, immunologic, or neurobehavioral) for these conditions, it is logical and necessary to continue a search, perhaps using models that rely on a more integrative approach, with stress and central nervous system responses as a final common pathway. Thus, many of the recommendations in this category refer to Figure 1, which is a model of the exposure–outcome relationship that passes through the systems of the human stress response, and can apply to any of the conditions discussed at this conference. Although this model fits for environmental exposures, it seems to be applicable to many external stressors that can challenge a person's ability to respond appropriately and effectively. Researchers need to focus on identifying important susceptibility factors and modifying factors, as well as ultimate changes in behavior, structure, and function. Exposures and outcomes should be elaborated across different unexplained illnesses, thereby defining common and illness-specific outcomes and triggers.

For example, researchers should examine whether the locus of sensory transduction (the processing of a peripheral nervous system signal about the environment into a central nervous representation) is in the same brain regions for various unexplained symptom syndromes. More specifically, investigators should probe the relationship, if any, between pre-existing and situational modifiers (Figure 1) and the CNS locus of sensory transduction.

This mechanistic model of the relationship between exposure, susceptibility, and symptoms further suggests that for multiple chemical sensitivity and other unexplained illnesses that appear to involve sensation of the environment through olfaction, or even other sensory modalities such as hearing and touch, classical conditioning

approaches should continue to be explored as important candidate mechanisms that can help explain the relationship of symptoms to the environment. It is important for investigators to deliver rigorously controlled and purified exposures to subjects, in a blinded fashion. This is a substantial challenge, given the low odor thresholds of many compounds of interest.

We agreed that reliance on quantitative measures of outcome that minimize susceptibility to experimenter bias needs to be developed; validated and combined neuroimaging techniques, discussed in the paper by Natelson and Lange (16), are one example. Markers of effect that can be used both in the laboratory and in the field need to be developed; for instance, common symptom scales, computerized neurobehavioral measures, and physiologic measures such as cortisol, heart rate variability, and neuroendocrine measures can be used in the field as well as in the laboratory.

We agreed that the importance of comparing and understanding individuals' beliefs (something one holds consciously) as well as their mental models (how one processes information and stimuli, which may be conscious or unconscious), should be explored (19,20). This would be true for

both patients and for practitioners. For example, exploration of why someone considers himself/herself "unusually sensitive" would be useful and can be approached through various qualitative research methods, including anthropological approaches.

Blinded experimental research is indicated, such as the double-blind randomized studies of electrical sensitivity (21). Because these symptomatic conditions affect substantial numbers of individuals, and because reasonable efficacy has been shown for some of them, further randomized controlled trials of cognitive behavioral therapy as a symptom management tool are indicated.

Animal models of unexplained illnesses need to be developed. In addition, since psychiatric co-morbidity is often seen in persons with unexplained illnesses, there is a need for good animal models of depression and anxiety.

Conclusions

Based on the recommendations of the experts present at this conference, it is clear that research must advance on many fronts to help us out of the quagmire that characterizes many public health situations in which medically unexplained symptoms appear to be present or are invoked. Perhaps we will find that

multiple mechanisms ultimately combine to contribute to these expressions of illness: environmental stressors, misperceptions, and disordered brain biochemistry to name a but a few. Thus, the methods for understanding MUS will ultimately require multidisciplinary approaches, bridging the gaps between those who investigate under an environmental causation paradigm and those who operate under a more traditional biopsychosocial paradigm and are largely ignorant of the complex roles of environmental factors. We hope that the breadth of support for this conference augurs for increased recognition of the common challenges presented as we attempt to understand what lies beneath the enigma of Medically Unexplained Symptoms and their relationship to the Environment (MUSE).

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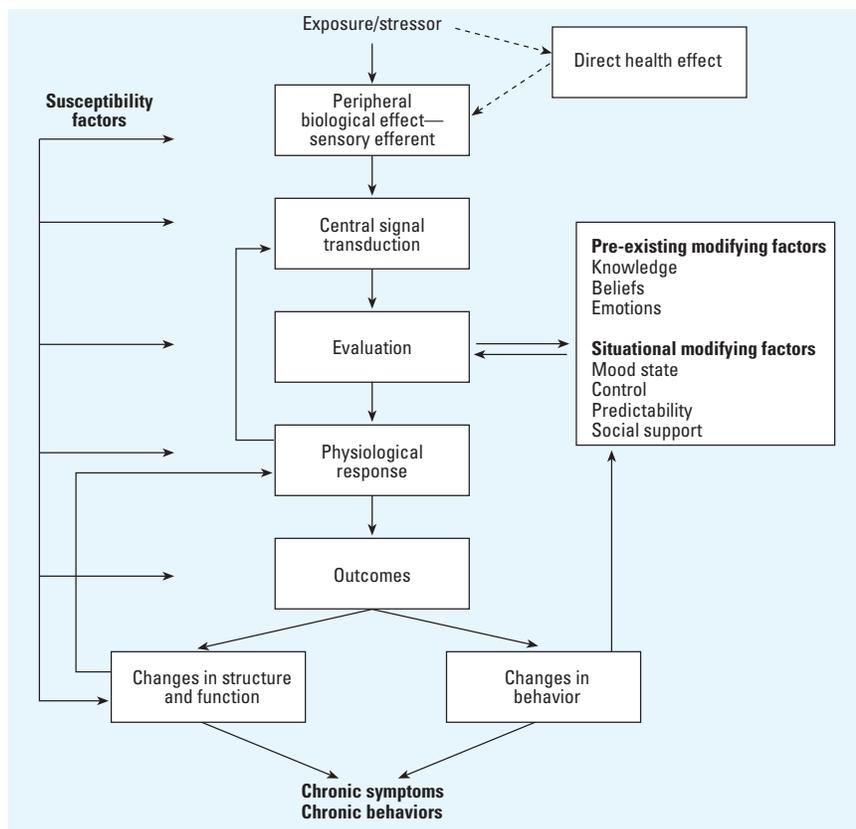


Figure 1. Mechanistic model of the interrelationships between exposures, susceptibility, and symptoms.

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